Carbonated Soft Drink Consumption and Risk of Esophageal Adenocarcinoma

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Carbonated soft drinks (CSDs) have been associated with gastroesophageal reflux, an established risk factor for esophageal adenocarcinoma. As both CSD consumption and esophageal adenocarcinoma incidence have sharply increased in recent decades, we examined CSD as a risk factor for esophageal and gastric cancers in a U.S. multicenter, population-based case-control study. Associations between CSD intake and risk were estimated by adjusted odds ratios (ORs), comparing the highest versus lowest quartiles of intake. All statistical tests were two-sided. Contrary to the proposed hypothesis, CSD consumption was inversely associated with esophageal adenocarcinoma risk (highest versus lowest quartiles, OR = 0.47, 95% confidence interval = 0.29 to 0.76; P_{trend} = .005), due primarily to intake of diet CSD. High CSD consumption did not increase risk of any esophageal or gastric cancer subtype in men or women or when analyses were restricted to nonproxy interviews. These findings indicate that CSD consumption (especially diet CSD) is inversely associated with risk of esophageal adenocarcinoma, and thus it is not likely to have contributed to the rising incidence rates. [J Natl Cancer Inst 2006;98:72–5]

Incidence rates for esophageal adenocarcinoma have increased >350% since the mid-1970s *(1)*. It has been suggested that carbonated soft drinks (CSDs) may have contributed to the increasing trend of esophageal adenocarcinoma because of a parallel increase in consumption of CSDs, the acidic nature of these drinks (pH<4.0), and their capacity to increase gastric distension *(2)*. Also, CSDs have been positively associated with nocturnal heartburn *(3)*. Despite media reports of a link between CSD consumption and esophageal cancer risk *(4)*, this association has not been evaluated in analytical epidemiologic studies. We utilized data from a large U.S. study of esophageal and gastric cancer, including esophageal adenocarcinoma, to evaluate this association.

A detailed description of the methods used is available elsewhere *(5,6)*. Briefly, this multicenter, population-based case–control study was conducted in three geographic areas of the United States—the state of Connecticut, a 15-county area of New Jersey, and a three-county area of western Washington state. The study included four incident case groups (esophageal adenocarcinoma, gastric cardia adenocarcinoma, esophageal squamous cell carcinoma, and noncardia gastric adenocarcinoma), and population control subjects. Control subjects aged 30–64 years were identified by random digit dialing, and those aged 65–79 years were identified through Health Care Financing Administration rosters. Institutional review board approval was obtained from all participating centers.

After obtaining written consent, interviewers administered an in-person structured questionnaire *(6)*. Subjects were

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asked about their usual frequency of consumption of "diet soft drinks or soda" and "regular soft drinks or soda, not diet" (per day, week, month, or year) during the period 3–5 years before diagnosis (case patients) or interview (control subjects). Frequencies for these items were combined to estimate total consumption. Data on duration of intake were not available.

This analysis includes 687 control subjects, 282 case patients with esophageal adenocarcinoma, 255 with gastric cardia adenocarcinoma, 206 with esophageal squamous cell carcinoma, and 352 with noncardia gastric adenocarcinoma.

The exposure variable, CSD consumption, was categorized into quartiles based on the distribution among control subjects and ranked from low (quartile one [Q1]) to high (quartile four [Q4]). We examined several factors associated with CSD consumption in our controls, comparing Q4 versus Q1 consumers. Chi-squared values and Student's *t* test were used for examining statistical significance. Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for each of the case groups compared with the control subjects in relation to quartile of CSD consumption, adjusting for design variables, with further adjustment for known risk factors such as smoking, drinking, body mass index, and reflux (see Table 2 footnote for a complete list of confounders included in the analysis). Tests for linear trend were evaluated by assigning each subject the median number of CSDs consumed in the quartile and treating that as a continuous variable in the logistic model.

Despite efforts to interview case patients rapidly after diagnosis *(5,6)*, proxy interviews were required for approximately 30% of case patients and 3% of control subjects. The validity of reported CSD consumption may be poorer for proxy respondents; therefore, we repeated analyses for self-interviewed subjects only. Gastroesophageal reflux disease is an established risk factor for esophageal adenocarcinoma *(7,8)*, and subjects with chronic reflux might have altered their CSD consumption; therefore, we also repeated analyses restricted to subjects with no reported reflux symptoms. Stratified analyses were also performed for men and women. All tests for statistical significance were two-sided, and $P<.05$ was considered statistically significant.

Among control subjects, high (Q4) CSD consumers were statistically significantly younger (59 years versus 65 years, $P<.001$), had greater mean adult body mass index (25.8 kg/m^2 versus 24.7 kg/m^2, $P = .002$), had greater caloric intake (2080 kcal/day versus 1770 kcal/day, $P<.001$), and consumed more meat (2.2 servings per day versus 1.9 servings per day, $P = .007$) than low (Q1) CSD consumers (Table 1). High (Q4) CSD consumers reported higher income ($P = .08$) and more reflux symptoms ($P = .07$) than low (Q1) CSD consumers.

In unadjusted regression analyses, high CSD consumption was associated with a statistically non-significant reduction in the risk of esophageal adenocarcinoma (Q4 versus Q1, OR = 0.71, 95% CI = 0.49 to 1.03). After adjustment for design variables and known risk factors, this association became statistically significantly inverse (Q4 versus Q1, adjusted OR = 0.47, 95% CI = 0.29 to 0.76; $P_{trend} = .005$) (Table 2). An inverse association between high CSD consumption and risk of noncardia gastric adenocarcinoma was suggested (Q4 versus Q1, OR = 0.65, 95% CI = 0.43 to 0.98; $P_{trend} = .06$). Analyses restricted to subjects with nonproxy interviews, or to persons without reflux symptoms, showed results similar to those in the overall study population (Table 2). High CSD consumption was associated with a similarly reduced risk of esophageal adenocarcinoma in men and women, although the trend for women was not statistically significant (Table 2).

We analyzed consumption of diet CSDs and regular (non-diet) CSDs separately. Forty-two percent of control subjects did not consume regular CSDs, and 60% did not consume diet CSDs (20% consumed no CSDs of either type); therefore, we estimated the risk associated with the top 20% of intake compared with no intake of each type of

Table 1. Characteristics of control subjects reporting high (quartile 4 [Q4]) versus low (quartile 1 [Q1]) consumption of total carbonated soft drinks

Characteristic	Q1 (<1 drink/month) *n* = 160	Q4 (≥1 drink/day) *n* = 191	*P**
Center, %			.91
CT	29.4	31.4	
NJ	51.3	50.3	
WA	19.4	18.3	
Sex, % male	78.1	82.2	.34
Race, % nonwhite	3.8	5.8	.38
Proxy, % completed by proxy respondent	1.9	3.7	.32
Income, %			.076
<$15 000	17.5	10.5	
$15 000–$29 999	26.9	25.1	
$30 000–$49 999	23.8	25.7	
$50 000–$74 999	20.6	16.8	
$75 000–$99 999	5.6	10.5	
≥$100 000	5.6	11.5	
Education			.79
<8 years	3.1	2.6	
8–11 years	17.5	15.2	
12 years	23.8	27.2	
Vocational/technical	9.4	8.9	
Some college	15.6	19.9	
College graduate	18.1	13.1	
Graduate school	12.5	13.1	
Reflux symptoms			.069
Never	61.3	49.7	
1–2 times/year	11.3	10.5	
3–12 times/year	10.6	11.5	
13–104 times/year	10.6	13.6	
105–364 times/year	4.4	6.3	
≥365 times/year	1.9	8.4	
Mean age, year	65.0	59.3	<.001
Mean adult BMI, kg/m^2	24.7	25.8	.002
Mean caloric intake, kcal/day	1770	2080	<.001
Mean servings of meat/day	1.9	2.2	.007
Mean servings of vegetables/day	3.6	3.3	.13

**P* values (two-sided) were calculated using the chi-square test (categorical variables) or Student's *t* test (continuous variables).

Table 2. Adjusted* odds ratios and 95% confidence intervals for association between carbonated soft drink consumption and risk of esophageal and gastric cancer subtypes†

Group	N	Odds ratios (95% confidence intervals) by quartile				P_{trend}§
		Q1‡	Q2	Q3	Q4	
Total						
Control subjects	687					
EA	282	1.00 (referent)	0.65 (0.40 to 1.07)	0.58 (0.36 to 0.92)	0.47 (0.29 to 0.76)	.005
GC	255	1.00 (referent)	0.86 (0.52 to 1.40)	0.97 (0.62 to 1.51)	0.74 (0.46 to 1.16)	.23
ES	206	1.00 (referent)	1.27 (0.71 to 2.28)	0.81 (0.46 to 1.44)	0.85 (0.48 to 1.52)	.33
OG	352	1.00 (referent)	0.79 (0.52 to 1.21)	0.78 (0.52 to 1.16)	0.65 (0.43 to 0.98)	.06
Men						
Control subjects	549					
EA	235	1.00 (referent)	0.64 (0.37 to 1.12)	0.68 (0.41 to 1.13)	0.46 (0.27 to 0.79)	.01
GC	217	1.00 (referent)	0.87 (0.50 to 1.52)	1.19 (0.73 to 1.94)	0.83 (0.50 to 1.38)	.54
ES	166	1.00 (referent)	1.39 (0.71 to 2.71)	0.89 (0.46 to 1.73)	0.99 (0.52 to 1.90)	.63
OG	244	1.00 (referent)	0.88 (0.53 to 1.45)	0.81 (0.51 to 1.30)	0.62 (0.38 to 1.01)	.06
Women						
Control subjects	138					
EA	47	1.00 (referent)	0.60 (0.17 to 2.18)	0.15 (0.03 to 0.73)	0.40 (0.10 to 1.55)	.19
GC	38	1.00 (referent)	1.35 (0.40 to 4.54)	0.51 (0.14 to 1.82)	0.46 (0.12 to 1.74)	.14
ES	40	1.00 (referent)	1.57 (0.37 to 6.71)	0.58 (0.14 to 2.48)	0.36 (0.08 to 1.71)	.12
OG	108	1.00 (referent)	0.45 (0.18 to 1.09)	0.64 (0.28 to 1.47)	0.63 (0.27 to 1.46)	.55
Nonproxy						
Control subjects	667					
EA	195	1.00 (referent)	0.65 (0.38 to 1.10)	0.62 (0.38 to 1.02)	0.47 (0.28 to 0.78)	.001
GC	189	1.00 (referent)	0.93 (0.56 to 1.55)	1.02 (0.64 to 1.62)	0.75 (0.46 to 1.22)	.24
ES	135	1.00 (referent)	1.38 (0.75 to 2.55)	0.86 (0.47 to 1.58)	0.79 (0.42 to 1.47)	.21
OG	246	1.00 (referent)	0.83 (0.53 to 1.29)	0.83 (0.55 to 1.26)	0.69 (0.45 to 1.07)	.13
No reflux						
Control subjects	367					
EA	112	1.00 (referent)	0.81 (0.41 to 1.60)	0.56 (0.28 to 1.14)	0.43 (0.21 to 0.90)	.02
GC	151	1.00 (referent)	1.06 (0.57 to 1.99)	1.30 (0.74 to 2.30)	0.76 (0.42 to 1.39)	.33
ES	158	1.00 (referent)	1.33 (0.66 to 2.65)	0.71 (0.35 to 1.42)	1.00 (0.51 to 1.98)	.69
OG	201	1.00 (referent)	0.74 (0.42 to 1.31)	0.97 (0.59 to 1.62)	0.66 (0.38 to 1.14)	.23

*Full model adjusted for age; sex; center (Connecticut, New Jersey, or Washington); race (white, nonwhite); proxy interview status (proxy or self-report); average adult body mass index; mean caloric intake; consumption of beer, wine, and liquor (each); consumption of meat; cigarettes per day; education (<8 years, 8–11 years, 12 years, vocational/technical, some college, college graduate, or graduate school); income (<$15 000, $15 000–$29 999, $30 000–$49 999, $50 000–$74 999, $75 000–$99 999, or ≥$100 000); and frequency of reflux symptoms (never, 1–2 times/year, 3–12 times/year, 13–104 times/year, 105–364 times/year, or ≥365 times/year). Stratified analyses eliminated covariates (e.g., sex, proxy status, reflux) as appropriate.

†EA = esophageal adenocarcinoma; GC = gastric cardia adenocarcinoma; ES = esophageal squamous cell carcinoma; OG = noncardia gastric adenocarcinoma.

‡Quartile cutpoints (drinks/year total carbonated soft drinks) were as follows: Q1 = 0–11, Q2 = 12–103, Q3 = 104–364, Q4≥365.

§P_{trend} values (two-sided) were calculated using the chi-square test after assigning each subject the median number of carbonated soft drinks consumed in the quartile and treating that as a continuous variable in the logistic model.

beverage. There was no evidence that high consumption of either type of beverage was associated with an increased risk of any of the cancer types. Indeed, high consumption of diet CSDs (OR = 0.52, 95% CI 0.32 to 0.83), but not regular CSDs (OR = 0.84, 95% CI = 0.52 to 1.37), was associated with a statistically significantly lower risk of adenocarcinoma of the esophagus. High consumers of diet CSDs also had a statistically significantly reduced risk of the other tumor types (esophageal squamous cell carcinoma OR = 0.43, 95% CI = 0.23 to 0.82, P = .02; gastric cardia adenocarcinoma OR = 0.50, 95% CI = 0.31 to 0.81, P = .01; noncardia gastric adenocarcinoma OR = 0.58, 95% CI = 0.38 to 0.90, P = .01) than nonconsumers. In contrast, no association was observed between regular CSD consumption and any tumor type. Among control subjects, consumers of diet CSDs were more likely to be white, have higher income and body mass index, and consume fewer calories than nonconsumers.

Consistent with the report of others *(3)*, we observed more frequent self-reported reflux symptoms in participants who consumed more CSDs than in those who consumed less (Table 1). Despite this association and after adjustment for confounding factors, there was no evidence that CSD intake was associated with an increased risk of esophageal adenocarcinoma or any other type of esophageal or gastric cancer. Rather, our data suggested an inverse association for esophageal adenocarcinoma.

The study has several limitations. As in any case-control study, recall bias must be considered; however, it seems unlikely that case patients would be less likely to recall CSD consumption than control subjects, especially diet CSDs. Also, intake of CSDs 3–5 years prior to diagnosis might not reflect intake in the distant past, particularly for persons with reflux who might have reduced their intake of CSDs. Arguing against this, however, is the finding that CSD intake was inversely associated with esophageal cancer risk in case patients without reflux symptoms. Although a true inverse association of diet CSDs and risk of esophageal adenocarcinoma cannot be ruled out, an alternative explanation is that diet CSD consumers differ from nonconsumers with regard to other unmeasured health behaviors that reduce risk.

The large sample size is one of the study's strengths. Population-based study design, in-person interviews, and ability to control for confounders are others.

Esophageal adenocarcinoma is a largely preventable cancer. Our previous results indicate that cigarette smoking, excessive body mass index, history of gastroesophageal reflux, and low fruit and vegetable consumption account for a combined population attributable risk of 80% *(9)*. The current study provides no evidence that avoidance of CSDs would be an effective strategy to lower the incidence of esophageal adenocarcinoma.

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Notes

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